AMENDMENTS TO THE SPECIFICATION:

Amend the specification as follows:

Delete the paragraphs spanning lines 23-35 of Page 37 and insert the following new paragraphs therefor:

Figure 1: This relates to the diagrammatic representation of the natural peptide L-IRGERA (SEQ ID NO:18) and of peptide analogues.

Figure 2: This relates to the ELISA test of the immune response to the four peptide analogues injected as peptides coupled to SUV in BALB/c mice. The antisera are diluted 1:500 and tested with homologous peptides (A and B) or with H3 (parent protein) (C, D). The anti-murine IgG conjugate (H + L) revealing murine antibodies of isotypes IgG1, IgG2a and IgG2b (blank symbols) and the anti-murine IgG3 conjugate (solid symbols) are both diluted 1:5,000. The results represent the mean values of the absorbance obtained in each group of two mice immunized with the peptide L-IRGERA (SEQ ID NO:18) (Δ, ▲), the retro-inverso peptide (o,•), the D peptide (□, ■) and the retro peptide (◊ , ♦). The arrows indicate the immunization plan for the mice.

Delete the paragraph spanning lines 10-13 of Page 38 and insert the following therefor:

Figure 4: This relates to the synthesis of the retro-inverso analogue of the C-terminal epitope of the protein H3: IRGERA (SEQ ID NO:18).

Sequence of the parent peptide (SEQ ID NO:5):

[H Cys-Gly-Gly]-Ile-Arg-Gly-Glu-Arg-Ala-OH

Delete the paragraph spanning lines 35-36 of page 39 and insert the following therefore:

Figure 10 shows the list of peptides synthesized for the therapeutic immunomodulation tests (wherein Gly Ile Leu Gly Phe Val Phe Thr Leu is (SEQ ID NO:3); Gly Leu Leu Gly Phe Val Phe Thr Leu is (SEQ ID NO:19); and Gly Ile Leu Gly Phe Val Phe Ala Leu is (SEQ ID NO:20)).

Delete the paragraph spanning line 13 of Page 43 through line 8 of page 44 and insert the following therefor:

Three analogues of model peptides of the IRGERA (SEQ ID NO:18) sequence corresponding to COOH-terminal residues 130 to 135 of the histone H3 are prepared. The preparation and purification of the L- and D-IRGERA (SEQ ID NO:18) peptides have been described previously (Benkirane et al., (1993), J. Biol. Chem., **268**, 26279-26285). The two new analogues, the retro-inverso peptides and the retro peptides, are synthesized in the same way as the L and D peptides by the solid phase method on a

multi-channel peptide synthesizer (Neimark, J. & Briand, J.P., (1993), Peptide Res., **6**, 219-228). The retro-inverso and retro isomers modified at the terminal ends are linked, using the protective group Boc, on a p-methylbenzhydrylamine resin (Applied Biosystem, Roissy, France). Linkage of the protected peptide chain is effected on a scale of 200 μmol using the *in situ* neutralization protocol described previously (Neimark, J. & Briand, J.P., (1993), Peptide Res., **6**, 219-228). The monobenzyl ester of (R-S)-2-methylmalonic acid obtained by alcoholysis of 2,2,5-trimethyl-1,3-dioxane-4,6-dione (Chorev et al., (1983), J. Med. Chem., **26**, 129-135) is incorporated into the peptide chain in racemic form. Coupling is monitored by the ninhydrin test. After this last coupling, the peptide-resin is washed twice with ether and dried in vacuo in a desiccator. The peptides are cleaved from the resin by treatment with anhydrous HF comprising 10% (v/v) of anisole and 1% (v/v) of 1,2-ethanedithiol. After removal of the HF in vacuo, the peptides are extracted from the resin and lyophilized. The crude peptides are then purified over a C18 column using a medium pressure apparatus (Kronwald Separation Technology, Sinsheim, FRG), by elution with a linear gradient of from 5 to 50% (v/v) of acetonitrile in 0.06% aqueous trichloroacetic acid. The purity of each fraction is determined by analytical passes over a column of Novapak C18 of 5 μm (3.9 x 150 mm), using a linear gradient of from 7 to 32% (v/v) of acetonitrile in an aqueous 0.1 M triethylammonium phosphate buffer. The passes are effected with a Waters apparatus (Waters Corporation, Milford, MA). The fractions comprising the pure mixture of diastereoisomers are collected and lyophilized. The mass spectra are obtained on a VG ZAB-2SE double concentration analytical instrument and recorded on a VG 11-250 data system (VG Analytical, Manchester, UK) as described (briand et al.,

(1989), Peptide Res., **2**, 381-388). The circular dichroism measurements are carried out as described in (Benkirane et al., (1993), J. Biol, Chem., **268**, 26279-26285).

Delete the paragraph spanning lines 1-18 of Page 44 and insert the following therefor:

In order to place the peptides on a plate to carry out a direct solid phase ELISA test, the IRGERA (SEQ ID NO:18) analogues are first conjugated to BSA using N-succinimidyl-3-[2-pyridyl-dithio]-propionate (SPDP) as described previously (14). For immunization of mice, the peptides are coupled covalently to preformed small unilamellar liposomes (SUV) containing: 4-(p-maleimidophenyl)-butyrylphosphatidyl-ethanolamine (MBP-PE). Monophosphoryl-lipid A (MPLA) is incorporated into the SUV as an adjuvant (Benkirane et al., (1993), J. Biol. Chem., **268**, 26279-26285; Friede et al., (1993), Molec. Immunol., **30**, 539-547).

Delete the paragraph spanning lines 16-19 of Page 45, and insert the following therefor:

In addition, two other monoclonal antibodies 4x8 and 4x10 (JBC, vol 270, No. 20, May 19, 1995, pp. 11921-11926) were also obtained, and the affinity constant of these antibodies with respect to the L-IRGERA (SEQ ID NO:18) and retro-inverso IRGERA (SEQ ID NO:18) peptide was measured. The results are given below (Table 2).

Delete the paragraph spanning lines 13-20 on Page 47 and insert the following therefor:

Four peptides are used in this study (Figure 1). The parent peptide IRGERA (SEQ ID NO:18) corresponds to the COOH-terminal end of the histone H3 which has been studied previously (Friede et al., (1993) Molec. Immunol., **30**, 539-547; Muller et al., (1982), EMBO J., **1**, 421-425; Briand et al., (1992), J. Immunol. Meth., **156**, 255-265). One cysteine and two additional glycine residues are added to the NH_2-terminal end to allow selective conjugation of the peptides to liposomes or to BSA and to increase the accessibility of peptides bonded to the support.

Delete the paragraphs spanning lines 17-33 on page 48 and insert the following therefor:

Polyclonal antibodies to the IRGERA (SEQ ID NO:18) analogues

Groups of two BALB/c mice are injected with the four IRGERA (SEQ ID NO:18) analogues conjugated to liposomes. The reaction of the antibodies to the four peptides with the peptide analogues and with H3 is measured in a direct ELISA test. In this test, H3 and the four peptide analogues conjugated to BSA by means of SPDP are used to cover the plates. As shown on Figures 2A and 2B, a strong antibody response to the four peptides is obtained in the immunized mice. In the case of the L peptide, the antibodies belong to the IgG1, 2a and 2b subclasses. The IgG3 antibody response

appears slightly later (blood sample 4) than the IgG1, 2a and 2b antibody response (blood sample 2). In the case of the retro-inverso, D and retro peptides, the IgG3 antibody response is predominant. The majority of the antibody subclasses give cross-reactions with the parent histone H3 (Figures 2C and 2D), with the exception of the IgG1, 2a and 2b antibody to the D peptide and the retro peptide (Figure 2D), which show very little reaction with H3. It should be noted that although the IgG3 antibody response with respect to the retro-inverso peptide and the retro peptide is particularly strong, the duration of the antibody response is similar to that induced to the L and D peptides.

3) the retro-inverso IRGERA peptide mimics the natural L peptide well, but mimics neither the D peptide nor the retro peptide, while the retro peptide mimics the D peptide well, but mimics neither the L peptide nor the retro-inverso peptide.

Delete the paragraphs spanning lines 11-26 on page 49 of the specification and insert the following therefor:

Monoclonal antibodies to the L- and D-IRGERA (SEQ ID NO:18) analogues

Several fusion experiments were carried out with spleen cells of BALB/c mice immunized with the various IRGERA (SEQ ID NO:18) analogues described previously (9). From all the monoclonal antibodies obtained, three antibodies were chosen on the basis of their ELISA reactivity with the four peptide analogues. MAb 4x11 (IgG1) is generated by splenocytes of a mouse immunized with the L peptide; it reacts in ELISA

with the L peptide and the retro-inverso peptide, but not with the D peptide and only weakly with the retro peptide. The monoclonal antibodies 11x2 and 11x7 (both IgG3) are generated by splenocytes of a mouse immunized with the D peptide; they react in ELISA with the four IRGERA analogues, as well as with the parent histone H3.

Delete the paragraph spanning lines 22-30 on page 50 of the specification and insert the following therefor:

Polyclonal anti-rabbit H3 antibodies to the D, RI IRGERA (SEQ ID NO:18) analogues and the parent peptide

Table 5 shows that the anti-parent protein (histone H3) antibodies are capable of recognizing the parent IRGERA (SEQ ID NO:18) peptide and its analogue, the RI peptide, in ELISA in an identical manner. This result opens up all the possibilities for use of the immunoretroids in diagnosis in all cases where detection of antibodies to an exogenous protein (for example in virology or microbiology) or endogenous protein (for example autoimmunity or neurodegenerative diseases) is required.

Delete the paragraph spanning lines 3-5 of page 52 and insert the following therefor:

Recognition in an ELISA competition test of the IRGERA (SEQ ID NO:18) peptide and IRGERA (SEQ ID NO:18) analogues by murine antibodies induced to the homologous peptides and peptide analogues

Delete the paragraph spanning lines 7-8, in the title of Table 2, on page 53, and insert the following therefor:

Kinetic constants and affinity constants at equilibrium of MAb 4x11, 11x2 and 11x7 for the four IRGERA (SEQ ID NO:18) analogues, and 4x8 and 4x10 for L-IRGERA (SEQ ID NO:18) and RI-IRGERA (SEQ ID NO:18).

Delete the paragraph in the title of Table 3 on page 54 and insert the following therefor:

Recognition in a competition test in the BIAcore system of the IRGERA (SEQ ID NO:18) peptide and the IRGERA (SEQ ID NO:18) analogues by the antibodies MAb 4x11, 11x2 and 11x7

Delete the paragraph in the title of Table 4 on page 55 and insert the following therefor:

ELISA reactivity of MAb 4x11, 11x2 and 11x7 with the four IRGERA (SEQ ID NO:18) analogues.

Affinity constants at equilibrium of the three MAb for the four analogues.

Delete the paragraph in the title of Table 5 on page 56 and insert the following therefor:

Reactivity of the anti-histone H3 (parent protein) antibodies induced in the rabbit with the L, D and RI IRGERA (SEQ ID NO:18) peptides.

Insert the attached Sequence Listing in place of the Sequence listing filed July 25, 2000.